Papers and Originals

Rubella Vaccine Trial in Children

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Summary: A study with RA 27/3 attenuated rubella virus vaccine (Plotkin strain) showed that this produced a significant antibody response in all of twenty-one vaccinated non-immune children without any appreciable marked clinical reactions. Serological examination of 53 non-immune and 29 immune siblings living in the same households failed to show any evidence of transmission of infection.

Introduction

A live attenuated rubella virus strain cannot be regarded as suitable for vaccine manufacture unless, when administered to susceptible subjects, it consistently produces satisfactory titres of rubella antibodies, does not generate undesirable clinical responses, and does not produce infection in susceptible seronegative contacts. Preliminary studies indicate that four strains of attenuated rubella virus may meet these criteria. They are the HPV-77 virus (Meyer *et al.*, 1966 ; Buynak *et al.*, 1968), the Cendehill strain (Huygelen and Peetermans, 1967 ; Martin du Pan *et al.*, 1968), the RA27/3 or Plotkin strain (Plotkin *et al.*, 1967, 1968), and the Benoit strain (Buynak *et al.*, 1968). The first three have already been administered to adults in Britain (Dudgeon *et al.*, 1969). This paper reports on clinical experience with the RA27/3 strain in the first rubella vaccine trials in children in Britain and Ireland.

Since at the time of this trial it could not be assumed that rubella-susceptible contacts would not be infected by a vaccine, it was necessary to take precautions against infection of pregnant women during the four to five weeks after vaccination. On the other hand, it was necessary to have rubella-susceptible persons in constant close contact with vaccinees in order to study the contagiousness of vaccine infection. To conform with these requirements the trial was carried out in a rural area of about 300 square miles (777 sq. km.) in Ireland. This area was deliberately chosen because it contained many large families with young children living on relatively isolated farms and with minimal contact between these and other families in the surrounding neighbourhood, especially during school holidays. Also it was felt that the family was the most appropriate unit in which to study the possible spread of virus from a vaccinated child to other siblings or contacts.

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Methods and Materials

Study Population.—The purpose and procedure of the investigation were initially explained in detail to 49 mothers of large isolated families at their homes. Thirty agreed to participate in the study. Blood samples were taken originally only from the mothers in these families, and the sera titrated for haemagglutination inhibition (H.A.I.) antibodies by the filter paper disc method (Draper and Kelly, 1969) and the standard method (Stewart *et al.*, 1967). Three mothers were found to be seronegative and their families were therefore excluded from the trial. Blood samples were then collected from the 150 children between 1 and 17 years of age in the remaining 27 families, but the H.A.I. tests indicated that in some families most or all of the children were immune to rubella. Eventually 19 families with a total of 104 children participated in these studies.

Vaccine.—The RA27/3 strain of rubella virus at the 25th passage level was received from Dr. S. Plotkin and was passaged twice at the Wellcome Research Laboratories to produce vaccine at the 27th passage level. To prepare the vaccine WI-38 cell cultures at the 30th passage level were inoculated with seed virus and incubated at 30° C. for one day. The fluid on the cells was then changed, the cultures were washed twice to remove calf serum, and the cultures were maintained on Eagle's basal medium with serum at 30° C. Multiple harvests made at five and eight days were pooled, stabilized, and freeze-dried in 1-ml. and 0·5-ml. volumes. The cells maintained their normal karyology, were not oncogenic to hamsters, and there were no adventitious agents detected in the vaccine. Ampoules of vaccine freeze-dried from 1-ml. and 0·5-ml. volumes contained $10^{3.2}$ and $10^{2.9}$ $TCID_{50}$ of virus respectively.

Results

Clinical Evaluation—Twenty-one non-immune girls and one immune girl from these 19 isolated rural families were vaccinated with 10^3 $TCID_{50}$ of the Plotkin strain rubella virus vaccine. These girls ranged in age from 15 months to 8 years, and in general were the youngest non-immune females in each family. Fifty-three of the siblings in the trial were non-immune ; 29 were immune (Table I). Each vaccinated child had at least one non-immune sibling living in the same house, except in families H and I, where the vaccinee lived in one house and her non-immune contact was a very close friend and playmate in a neighbouring dwelling a few yards away (Table II). All the vaccinated children were examined clinically between Day 8 and Day 12 after receiving the vaccine. Mild enlargement of the postauricular glands was noted in 13, and two had a transient rash between Day 8 and Day 10 (Table III). Symptoms encountered during the 21 days' postvaccination period included arthralgia of the hip in a girl aged 8 years.

She complained of hip pain on Days 8 and 9, and though it was sufficient to make her limp it did not cause any anxiety. The parents clearly attributed the pain to vaccination. Five other children complained of mild malaise on one day only, but otherwise no symptoms were noted among the vaccinees during the 21 days.

TABLE I

No. of Families	No. of Children Vaccinated		No. of Unvaccinated Siblings	
	Non-immune	Immune	Non-immune	Immune
19	21	1	53	29

TABLE II.—*Age and Immune State of Vaccinees and Siblings*

Family	Age in Years															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A		–	0			–	–				+					
B		0		–	0	–		+	+							
C	–	–					0	–	–							
D	–		0			–			–		–					
E		0								–	–		–			
F	0		–		+		+	+								
G	–			–				0		–	–	–				
H			0	–		+	+		+	+				+		
I	0							+			+			T	+	
J			0		–	–		0	–			+		+		
K		0		0		–					–		+			
L		0			–		–		–							
M		–	–			0		–		–						
N	–				0			+				+				+
O	0		+		+					+	–		+	+		
P		0	–			–		–	–					–		
Q				–		Ø		+		+		–		+	+	
R		0		–			–	–		–						
S	0 T –		–	–			–	–								

0 = Non-immune vaccinee. – = Non-immune contact. 0 = Immune vaccinee. + = Immune contact. T = Twins.

TABLE III.—*Clinical Reactions in 21 Non-immune Children Given RA27/3 Rubella Vaccine*

Nature of Reaction	No. of Children	Mean Day of Onset	Mean Duration
Palpable post-auricular cervical glands	13	Day 9	2 Days
Rash	2	Day 9	1 day
Malaise	5	Day 9	1 day
Arthralgia	1	Day 9	2 days

Laboratory Studies.—Blood samples were again obtained from all the vaccinees and their siblings 46 days after vaccination. These second filter paper disc blood samples and sera were titrated, coded, in parallel with samples obtained two weeks before vaccination. The results of the haemagglutination inhibition tests showed that all the non-immune girls given RA27/3 responded to vaccination, whereas all their non-immune unvaccinated siblings remained seronegative. The immune child given the vaccine showed no booster response and the immune siblings showed no significant rise in titre (Table IV).

TABLE IV

Pre-vaccination Test Titres	No. of Vaccinees and Siblings Grouped According to H.A.I. Test Titres 46 Days after Vaccination						
	10	20	40	80	160	320	640
10	53		4*	2*	11*	4*	
20							
40							
80				1			
160					3	1	
320				1	5	8	2
640					1	5	1
1,280						1* 1	

* Vaccinated children.

Discussion

An acceptable rubella virus vaccine should cause little if any clinical reaction and should induce lasting immunity without infecting close contacts. If a vaccine were prepared from an insufficiently attenuated virus, it would give rise to an infection which was transmissible to rubella-susceptible contacts. If over-attenuated the vaccine would be inadequate as an immunizing agent because of the low seroconversion rates and low post-vaccination antibody titres. Although it is desirable that the rubella virus should not be excreted from the nasopharynx after vaccination, so as to preclude the chance of infecting a pregnant woman, this attribute has been observed only after vaccination with an overattenuated strain (Buynak *et al.*, 1968). Nasopharyngeal excretion of virus therefore will occur in a proportion of subjects vaccinated with an effective vaccine strain. This characteristic is acceptable provided infection does not spread to contacts.

By vaccinating the youngest rubella-susceptible female children in large families and subjecting several rubella-susceptible siblings to intimate contact with the vaccinees, the conditions in favour of transmission of infection from vaccinees were maximal. Nevertheless, serological studies showed that infection was not transmitted by the vaccinees in any of the 19 families involving 53 rubella-susceptible contacts. The vaccine induced an immunizing infection in all the rubella-susceptible vaccinated children, with satisfactory postvaccination haemagglutinating antibody titres, though in general somewhat lower than those obtained in subjects who previously had rubella. The reactions caused by the vaccine were minimal apart from a mild degree of arthralgia for two days in an 8-year-old girl.

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